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Androgens and Liver Tumors: Fanconi's Anemia and Non-Fanconi's Conditions

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The association between anabolic androgenic steroids and liver tumors was first noted in patients with Fanconi's anemia (FA). The hypotheses which led to this review were as follows: (1) androgen-treated individuals who do not have FA are also at risk of liver tumors; (2) parenteral as well as oral androgens may be responsible for liver tumors; (3) FA patients develop liver tumors after smaller and briefer androgen exposure than non-FA individuals; (4) the risk of hepatic neoplasms may depend on the specific androgen. Medline and Web of Science were searched for all cases of liver tumors associated with androgens. Information from individual cases was entered into a spreadsheet and descriptive statistical analyses were performed. Thirty-six FA cases and 97 non-FA cases with both nonhematologic disorders and acquired aplastic anemia (non-FA AA) were identified. The most common androgens were oxymetholone, methyltestosterone, and danazol. Hepatocellular carcinomas (HCC) were more often associated with oxymetholone and methyltestosterone, while adenomas were associated with danazol. Tumors were reported in six patients who received only parenteral and not oral androgens. FA patients were younger than non-FA patients when androgen use was initiated, and the FA patients developed tumors at younger ages. Non-AA patients were treated with androgens for longer periods of time, compared with FA and non-FA AA patients. All patients on anabolic androgenic steroids are at risk of liver tumors, regardless of underlying diagnosis. The magnitude of the risk cannot be determined from currently available data, because the number of patients receiving androgens is unknown. Am. J. Hematol. 77:257–267, 2004. **Published 2004 Wiley-Liss, Inc.**[†]

Key words: androgens; anabolic steroids; liver tumors; hepatocellular carcinomas; hepatomas; adenomas

INTRODUCTION

Fanconi's anemia (FA) is an autosomal recessive disorder characterized by congenital abnormalities and aplastic anemia (AA); the estimated FA birth rate is 1 in 360,000 [1]. Patients with FA are at increased risk of developing specific neoplasms at much younger ages than their counterparts in the general population [2,3]. For example, the median age for the development of AA in FA patients is 7 years, compared with > 70 years in the general population [1,4]. Androgen treatment has been recommended for FA patients with AA for whom there is no acceptable hematopoietic stem cell transplant donor. Oxymetholone, a 17-α-alkylated androgen, is the androgen used most often in FA and it is one of four anabolic androgenic steroids (AAS) currently in common use in the United States (the others are oxandrolone, stanozolol, and nandrolone decanoate) [5]. The association between androgens and liver tumors in FA was initially ascribed to the use of a potentially oncogenic agent in patients with a DNA instability syndrome [6].

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The possible connection between AAS and liver tumors was first noted in the 1960s in patients with FA who had been treated for AA [7,8]. Only one of the reported 37 patients with FA and liver tumors [2] did not receive androgen therapy [9]. The causal association between 17-α-alkylated androgens and hepatic tumors was inferred from observations of regression of hepatic lesions upon discontinuation of the AAS. Long duration of therapy and high doses of AAS were implicated in the risk of hepatocellular carcinomas (HCC). The relationship between 17-α-alkylated androgens and the development of malignant HCC is not clear in some cases, however, because of the short duration of the androgen exposure, the rarity of elevated α-fetoprotein, and a benign course in some patients [6,10–12]. The identification of a liver neoplasm as benign (usually adenoma) or malignant (usually HCC) is not always clear, either from the original article, or from clinical and pathologic review, and may vary from one hepatic area to another in the same patient [5,10].

The role of androgens in the etiology of liver tumors in individuals who do *not* have FA has not been examined comprehensively, although nearly 100 cases have been reported. The hypotheses which were addressed in this literature review were as follows: (1) androgen-treated individuals who do not have FA are also at risk of liver tumors; (2) parenteral as well as oral androgens may be responsible for liver tumors in non-FA as well as FA cases; (3) FA patients are more sensitive to the hepatic oncogenic properties of androgens and thus develop tumors on shorter courses and/or smaller cumulative doses than non-FA cases; and (4) the risk of hepatic neoplasms may depend on the specific androgen to which patients were exposed.

To our knowledge, there is no database that would provide data on the frequency of androgen administration in any disease. Thus, our analysis is descriptive, based on published cases, and lacks information on incidence or prevalence of liver tumors associated with androgens.

METHODS

The medical literature was searched for all reports of liver tumors occurring in patients treated with androgens, using Medline and Web of Science, and supplemented from the bibliographies of each publication. The initial search terms were "androgens" or "anabolic androgenic steroids", combined with "liver tumor", "liver cancer", "hepatoma", "adenoma", "hepatocellular carcinoma", or "liver neoplasm". Subsequent searches included each of the individual major androgens that were identified in the initial search (oxymetholone, methyltestosterone, and danazol) and others that were mentioned in any article, combined with the same liver tumor terms. The key phrase "oral contraceptives" was not included in the search terms because the focus was on anabolic agents which were previously implicated in FA. All languages were included, and articles were read in the original languages or after translation. For the sake of completeness, all references are cited for patients who were reported more than once, although such cases were counted only once in our analyses.

For patients who used more than one androgen, analyses were performed using the androgen which was received either for the longest duration or the largest cumulative total dose, if the duration was not stated. The cumulative time on androgen was determined from the ages at the start and the end of use of any androgen, unless otherwise stated in the report. The first liver tumor was scored in patients who developed more than one tumor, and those with HCC and adenoma at the same time were categorized as HCC unless the adenoma was substantially larger or there were multiple adenomatous lesions. Some reports were incomplete with regard to some of the information, and thus the analyses do not always include the same numbers of patients.

Information from individual cases was entered into Lotus 123 and Excel spreadsheets and subsequently transferred into Stata8, which was used for all statistical analyses [13]. Continuous distributions were compared using Student's *t*-test, and Fisher's exact test was used for comparisons of frequency data in different groups. Deviations of sex ratios from 1:1 were tested using the binomial probability test.

RESULTS

It is clear that patients with FA are not the only individuals who develop liver tumors following treatment with androgens: our review identified reports of tumors in 97 patients who received androgens for diagnoses other than FA (Table I). These included 40 with non-FA aplastic anemia (non-FA AA) and 57 with other diagnoses (non-AA), such as other forms of anemia, endocrine or gynecologic conditions, body builders, hereditary angioedema, immune thrombocytopenia, and others. There was a significant excess of males (65 males, 27 females, 5 unstated, $P = 0.00005$) in the non-FA patients, due primarily to the use of androgens in males with endocrine disorders, aplastic and other anemias, and body builders. The apparent excess of males in the FA group (22 males, 14 females) was not significant ($P = 0.12$).

The majority of the androgens belonged to the category of oral 17-α-alkylated derivatives (Table II). Other androgens included oral 1-methyl- and intramuscular 17-β-ester derivatives. In a few cases, the androgen was reported only as "anabolic androgenic steroids".

TABLE I. Categories of Androgen Recipients*

Group	Category	Subcategory	Indication	Total Number	M	F	NA	References
FA				36	22[a]	14	0	Summarized in [2]
Non-FA Conditions	Total			97	65[b]	27	5	
	Non-FA AA			40	26[b]	11	3	[6,10,14–35]
	Non-AA	Total		57	39[b]	16	2	
		Anemia	Paroxysmal nocturnal hemoglobinuria, refractory macrocytic, sideroblastic, renal, Diamond-Blackfan	10	8	1	1	[10,12,36–46]
		Endocrine	Hypogonadism, hypopituitarism, cryptorchidism, impotence, gynecomastia	21	21[b]	0	0	[12,32,36,47–56]
		Gynecologic	Irregular menses, menopause, menorrhagia, endometriosis, fibroids, trans-sexual	9	0	9	0	[52,57–66]
		Body builder		4	4	0	0	[67–70]
		Hereditary angioedema		5	2	3	0	[71–73]
		Immune thrombocytopenia		4	1	2	1	[33,45,74,75]
		Other	Multiple myeloma, osteoporosis, general weakness, systemic lupus erythematosus	4	3	1	0	[32,42,52,76]

*Abbreviations: M, males; F, females; NA, not available; FA, Fanconi's anemia; AA, aplastic anemia.
[a]M > F not significant ($P = 0.12$).
[b]M > F significant. Total non-FA group, $P = 0.00005$; AA, $P = 0.04$; non-AA, $P = 0.004$.

TABLE II. Types of Androgens Associated With Liver Tumors[a]

Category	FA	Non-FA
17-α-Alkylated (oral)	Oxymetholone Methyltestosterone Norethandrolone Methandienone Oxandrolone	Oxymetholone Methyltestosterone Danazol Methandrostenolone Norethandrolone Fluoxymesterone Stanozolol Ethylesterenol Methandienone Oxandrolone
1-Methyl (oral)	Methenolone	Methenolone Mesterolone
17-β-Ester (intramuscular)	Nandrolone decanoate Testosterone cipionate Testosterone enanthate Testosterone propionate	Nandrolone decanoate Testosterone enanthate Testosterone, not specified Nandrolone phenpropionate Testosterone propionate
Others not specified	Anabolic androgenic steroids	Anabolic androgenic steroids

[a]Androgens are listed in each category from the most frequent to the least frequently reported.

Oxymetholone was the most common androgen in the FA and the non-FA groups, while methyltestosterone and danazol were used frequently in non-FA patients. Danazol was not reported in either FA or non-FA AA but was used primarily in women with hereditary angioedema or immune thrombocytopenia. Many patients received more than one type of androgen, both concurrently and sequentially.

An unexpected finding was that six non-AA patients (4 males and 2 females) were reported to have received only parenteral and not oral androgens (Table III) [42,43,48,52,57]. The androgens were derivatives of testosterone or nandrolone. One patient had HCC, another developed multiple adenomas, 2 had cholangiocarcinomas, and 2 had angiosarcomas. The latter two were female, and both had also received oral contraceptive agents. It is impossible to determine whether the parenteral androgens or the oral contraceptives were of etiologic significance with regard to the unusual liver tumors in these two cases.

HCCs comprised 58% of the tumors in FA patients, 60% in non-FA AA patients, and 44% in the non-AA group, while adenomas were 36%, 30%, and 42%, respectively (Table IV). The excess of HCC in patients with AA, with or without associated FA, was not

TABLE III. Tumors in Non-AA Patients Who Received Only Parenteral Androgens

Age at tumor detection (years)	Sex	Androgen, duration	Indication	Tumors	Pathology	Status	References
Not stated	M	Testosterone, not stated	Hypogonadism	HCC	Biopsy	Alive 15 years later	[48,49]
32	M	Nandrolone phenpropionate, 1 year, Testosterone enanthate, 11 years	Alport's syndrome, anemia	Multiple adenomas	Needle biopsy	Alive at age 32 years	[43,44]
67	M	Testosterone enanthate, 3 years, Nandrolone decanoate, 1.2 years	Chronic renal failure	Cholangiocarcinoma	Autopsy	Died, not related to liver	[42]
68	M	Nandrolone decanoate, 2 years	Weakness	Cholangio-hepatocarcinoma	Laparotomy	Alive at age 68 years	[42]
57	F	Testosterone,[a] 2 years	Irregular menses	Angiosarcoma	Needle biopsy	Died 10 months later	[52,57]
58	F	Testosterone,[b] 8 years	Menopausal symptoms	Hemangiosarcoma	Laparotomy	Died 10 days postsurgery	[57]

[a]Received estrogen/progestin oral contraceptive 12 years prior to testosterone.
[b]Received estrogen/testosterone combination, followed by an oral contraceptive agent for 6 years.

TABLE IV. Diagnostic Categories and Types of Liver Tumors

Group	Category	Sex	Total number	HCC	Adenomas	Other tumors
FA		Total	36	21	13	2
		Male	22	14[a]	7[a]	1
		Female	14	7[a]	6	1
Non-FA Conditions		Total	97	49	36	12
		Male	65	35	20	10
		Female	27	12	13	2
		Not stated	5	2	3	
	Non-FA AA	Total	40	24	12	4
		Male	26	14	8	4
		Female	11	9	2	0
		Not stated	3	1	2	0
	Non-AA	Total	57	25	24	8
		Male[b]	39	21[a]	12[a]	6
		Female	16	3[a]	11	2
		Not stated	2	1	1	0

[a]Three FA and 3 non-AA patients had both HCC and adenomas. They are listed here according to the first and/or larger type of tumor.
[b]Male > female, $P = 0.01$.

significant compared with the non-AA subjects. There were two FA patients whose tumor types were not specified. Twelve of the patients in the non-FA group had "other tumors", which included cholangiohepatocarcinoma, cholangiocarcinoma, angiosarcoma, and tumors of types not specified. The excess of males with HCC was not significant in the FA or non-FA AA groups, but it was in the non-AA group ($P = 0.01$).

Three FA and 3 non-FA (non-AA) patients had both HCC and adenomas, either simultaneously or sequentially (Table V). Two of the FA patients had received oxymetholone (one was not stated), and 2 of the non-FA had received methyltestosterone, while the third had taken danazol. This small number of patients was heterogeneous with regard to their underlying diagnoses and types and duration of androgens.

The most commonly used androgens were oxymetholone, methyltestosterone, and danazol, either alone or in combination (Fig. 1). Twenty-three of the 36 FA patients had taken primarily oxymetholone. Among these, HCC comprised 57% and adenomas comprised 35% of the tumors. Two FA patients took methyltestosterone, and both developed HCC. Among 11 FA patients who took a variety of other androgens, 6 developed HCC and 5 developed adenomas.

Twenty-eight of the 97 cases in the non-FA group took oxymetholone, 21 took methyltestosterone, 15 took danazol, and 33 took other types of androgens. Sixty-four percent of those who took oxymetholone developed HCC, while 25% had adenomas. The distribution of tumors in those who took methyltestosterone was similar: 57% HCC and 33% adenomas. However, only 4 (27%) of the 15 patients who took danazol had HCC, while 11 (73%) had adenomas. Oxymetholone was the androgen used most often in the FA and non-FA AA patients, and the majority of the tumors were HCC. The excess of HCC in the non-FA patients on oxymetholone was significant compared with those on danazol ($P = 0.03$). Methyltestosterone was used primarily in non-AA patients, in whom it was also associated more commonly with HCC than with adenomas. Danazol was used only in patients without any form of aplastic anemia.

TABLE V. Cases With Both HCC and Adenomas

Group	Age at tumor detection (years)	Sex	Androgen	Indication	Duration (years)	Tumors	Pathology	Status	Reference
FA	12	F	Oxymetholone	AA	4	Multiple HCC nodules and several adenomas	Autopsy	Death, sepsis	[77]
	9	M	Oxymetholone	AA	3	Multiple large HCCs and small adenomas	Autopsy	Death, cerebral hemorrhage	[78]
	30	M	Not stated	AA	Not stated	Adenomas prior to bone marrow transplant; 15 years after transplant, died with HCC following hepatitis C	Not stated	Death, HCC	[79]
Non-FA (non-AA)	29	M	Methyltestosterone	Hypogonadism	11	Single 1.5-cm HCC and multiple adenomas	Surgery	Alive at age 31 years	[50]
	51	M	Methyltestosterone	Hypogonadism	20	HCC left lobe; 5 months after androgens stopped, multiple HCCs and adenomas right lobe	Surgery	Alive at age 53 years	[54]
	30	F	Danazol	Systemic lupus erythematosus	4	HCC left lobe, smaller adenoma right lobe	Surgery	Alive at age 31 years	[76]

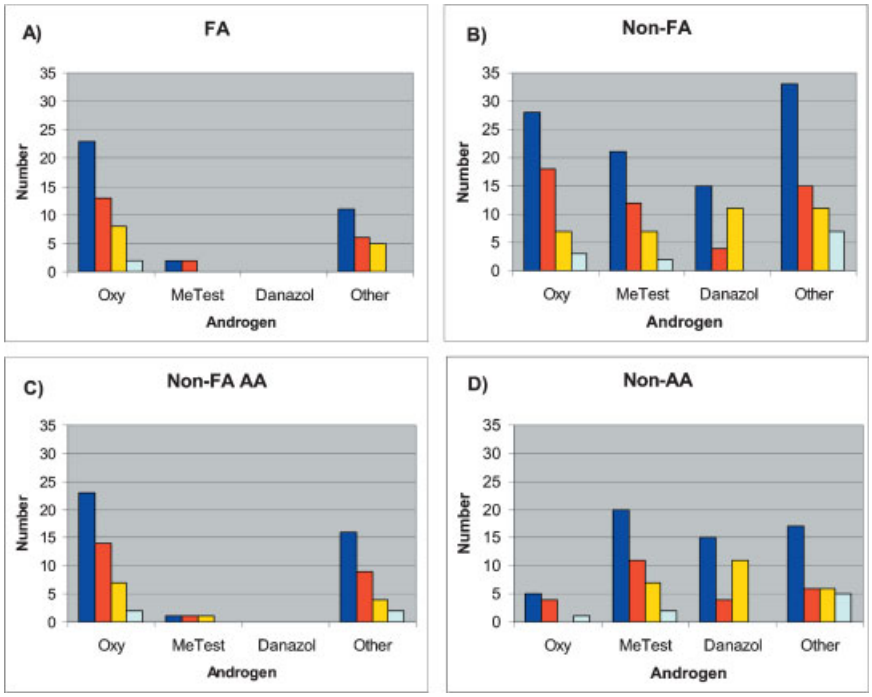

Fig. 1. Association between the type of androgen and the type of liver tumor. Figures show the numbers of patients using each type of androgen (black), the number who developed hepatocellular carcinomas (dark gray), the number who developed adenomas (light gray), and the number who developed other types of tumors (white). The androgens were oxymetholone (Oxy), methyltestosterone (MeTest), danazol (Dan), and others: (A) Fanconi's anemia (FA); (B) non-Fanconi's anemia (non-FA); (C) non-Fanconi's anemia aplastic anemia (non-FA AA); (D) non-aplastic anemia (non-AA). The excess of HCC with oxymetholone compared to danazol was significant in the non-FA group ($P = 0.03$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Data regarding the cumulative doses of the major androgens were available for 17 FA and 43 non-FA patients. The oxymetholone doses were similar in FA and non-FA patients, with respective medians of 73 and 65 g ($P = 0.3$). Only two FA patients received methyltestosterone, for total doses of 22 and 24 g, while in 13 non-FA patients the methyltestosterone median dose was 165 g. The median dose of danazol, reported in 13 non-AA cases, was 603 g. It is clearly difficult to compare drug types, doses, and tumor outcomes across multiple indications for use of androgens, except to suggest that equivalent doses of oxymetholone which were used in FA and in non-FA AA were associated with similar relative frequencies of HCC.

FA patients started androgens at much younger ages than either the non-FA AA or the non-AA patients. In those with HCC, FA patients were significantly younger than both the non-FA AA and the non-AA groups (median ages were 7.5, 13, and 25.5 years; $P = 0.03$ and 0.00004 for FA vs. non-FA AA and non-AA, respectively). The age distributions were similar in the patients with adenomas. The median ages were 7 years for FA, 10 years for non-FA AA, and 27 years for the non-AA patients. In this case, the FA and non-FA AA ages were not significantly different, while the non-AA were significantly older than both the FA and the non-FA AA patients ($P = 0.001$ and 0.0003). Within disease categories, the age at which androgens were started did not differ between HCC and adenomas.

The total duration of treatment with androgens prior to HCC was shorter in FA and non-FA AA (median 4 years in both groups, $P = 0.5$) than in the non-AA patients (median 5.6 years, $P = 0.02$ and 0.04 for FA and non-FA AA vs. non-AA respectively). The median duration prior to adenomas was also 4 years in FA, 5 years in non-FA AA, and 5.5 years in non-AA. The shorter treatment durations in the FA and non-FA AA hepatic adenoma groups were not statistically significant, although there was a trend toward a longer duration of treatment in the non-AA patients. The intervals from androgen initiation to tumor diagnosis were similar in the HCC and adenoma groups in each category.

Consistent with the early need for androgen treatment in FA patients with childhood-onset of AA, FA patients developed their liver tumors at younger ages than those with non-FA conditions. The median age

at diagnosis of HCC was 13.4 years in FA, 29 years in non-FA AA, and 48.5 years in non-AA; all differences were significant (FA vs. non-FA AA, $P = 0.006$; FA vs. non-AA, $P = 3 \times 10^{-8}$; non-FA AA vs. non-AA, $P = 0.02$). The median ages at adenoma diagnosis were 12, 18.1, and 37 years for the same groups, respectively. The ages at adenoma diagnosis for FA and non-FA AA were not significantly different, but both were younger than non-AA patients (FA vs. non-AA, $P = 2 \times 10^{-6}$; non-FA AA vs. non-AA, $P = 0.005$). There was no significant difference in age at diagnosis of HCC or adenoma for the FA and non-FA AA patients, although the non-AA patients with HCC showed a trend toward being older than the non-AA with adenomas ($P = 0.08$).

Six FA and four non-FA (non-AA) patients had tumors that were diagnosed after androgen therapy had been discontinued (Table VI). Five of the FA and only 1 of the non-FA patients had HCC, 1 adenoma was reported in each category, and angiosarcomas were seen in 2 non-FA patients. Androgens had been used for 4 months to 10 years in the FA patients, and the interval after androgens were discontinued ranged from 2 to 4 months in 3 patients and from 1 to 24 years in the others. The non-FA patients took androgens for 2–10 years, and the tumors were detected between 3 and 10 years after the androgens were stopped.

α-Fetoprotein (AFP) is a serum marker which is often elevated in HCC [80]. AFP was increased in 0/10 FA, 3/15 non-FA AA, and 1/12 non-AA in whom it was measured [14,33,58], as well as one non-AA case with cholangiohepatocarcinoma [67]. Additional risk factors for the development of cirrhosis and subsequent HCC, such as transfusion histories and titers of hepatitis B and C and other viruses, were described too infrequently for analysis.

DISCUSSION

Liver tumors associated with androgens were reported in nearly 100 patients with acquired AA and with non-AA disorders, as well as in 36 patients with FA. In FA patients, the cumulative probability of liver tumors has been previously estimated to be 46% by age 50 [2]. The cumulative risk of these tumors in non-FA patients cannot be determined from this review, since there is no registry of patients receiving androgens, and none of the reports provided any data regarding the numbers of androgen-treated patients who did not develop tumors. The majority of the FA and non-FA cases with liver tumors were male, although most of the treated hematologic disorders do not occur more frequently in males than females. The excess of males with liver neoplasms could be a reflection of a true difference in the relative number of male and female users of a medication with significant virilizing side effects. It is likely that the use of androgens for muscle building is more prevalent among males than females [86]. It is theoretically possible that males have a higher risk of hepatic neoplasia following androgen treatment than do females [87]. However, without a denominator, the male excess remains unexplained.

Independent of the indication for androgen therapy, HCC was reported more frequently in patients who received oxymetholone or methyltestosterone, rather than danazol, either as the only androgen or in combination with other androgens. Adenomas were reported more frequently in those patients treated with danazol. However, among the literature reports reviewed, danazol was used only in non-AA patients, while oxymetholone and methyltestosterone were used in FA and non-FA AA. Thus we cannot determine whether HCC was related to the type of androgen or to the underlying indication for androgen treatment. Inferences regarding a possible association between a specific androgen and a specific type of tumor are further complicated by the fact that the majority of the patients were exposed to more than one androgen. It should also be emphasized that six non-FA patients with hepatic neoplasms were reported to have received parenteral androgens, although the general perception is that liver tumors are associated only with oral androgens [5].

Oxymetholone was the only androgen for which there was sufficient data on cumulative dose for comparison between FA and non-FA patients, and the results suggest that the doses were not different. The doses of oxymetholone used in patients who developed HCC were similar to those used in patients who developed adenomas. Likewise, the doses of danazol associated with HCC and adenomas were similar. Comparisons between total grams of oxymetholone, methyltestosterone, and danazol are not meaningful because the therapeutic doses of each drug are different.

In general, FA patients develop AA at an early age; therefore, it is not surprising that the reported cases with FA started androgen treatment at a younger age than did those with non-FA disorders. Age at initiation of androgen therapy did not appear to be associated with whether the neoplasm was an HCC or an adenoma. In several of the FA and non-FA AA patients, liver tumors were only discovered at autopsy following death from complications of the primary disorder. The benign nature of the underlying conditions for which androgens were administered in the non-AA subjects makes it unlikely that autopsy diagnosis of an occult hepatic neoplasm would occur in this group. The age sequence at which tumors were diagnosed was, from youngest to oldest: FA, non-FA AA, and non-AA. This reflects a

TABLE VI. Liver Tumors Diagnosed After Discontinuation of Androgen Therapy

Group	Age at tumor detection (years)	Sex	Androgen	Indication	Duration of all androgens (years)	Interval after discontinued androgens (years)	Tumors	References
FA	27	M	Testosterone, testosterone enanthate	AA	4	1.4	HCC	[6,7]
	38	M	Not stated	AA	0.3	24	HCC	[81]
	12	M	Oxymetholone	AA	3	0.3	Adenoma	[82]
	9	M	Methyltestosterone	AA	4	0.4	HCC	[83]
	14	M	Testosterone, oxymetholone	AA	9	0.2	HCC	[84]
	31	F	Oxymetholone	AA	10	8	HCC	[85]
Non-FA (non-AA)	16	M	Stanazol, oxymetholone, testosterone enanthate	Sideroblastic anemia	6	3	Adenoma	[19]
	56	M	Fluoxymesterolone, other AAS	Osteoporosis	10	3	Angiosarcoma	[52]
	58	F	Testosterone (combined with estrogen)	Menopause	8	6	Angiosarcoma	[57]
	Not stated	Not stated	AAS	PNH	2	10	HCC	[31]

combination of the age at which androgens were begun and the duration of therapy.

There are clearly limitations to relying upon literature reports to evaluate the association of liver tumors with androgens. These include publication biases, in which those cases that were diagnosed with liver neoplasms may be over-reported, and the amount of under-reporting cannot be ascertained. There may also be reporting errors and missing data with regard to the type of androgen, the dose, and the duration. Another limitation is the reliability of specific reported tumor diagnoses since specimens were not reviewed centrally. The distinction between HCC and adenoma may not always be clear-cut, even to an experienced liver pathologist. The presence of an elevated AFP in only 4 of the 37 in whom it was measured does not help to distinguish HCC from adenomas. Because some patients had both types of tumors, misclassification could have occurred in patients with multiple hepatic masses in which only one lesion was actually biopsied. Our classification of patients with multiple tumors to HCC or adenoma based on the first and/or largest tumor may have been excessively arbitrary.

This review is purely descriptive, since there is no known denominator for the number of FA or non-FA patients who receive androgens. It is theoretically possible that some of the non-FA AA cases actually had FA, since only two articles mentioned absence of an FA phenotype, and none described negative results of the chromosome breakage test, which is used to confirm the diagnosis of FA. However, the non-FA AA patients were significantly older than those with FA when they began androgen therapy, and when they developed liver tumors. A prospective study of non-FA patients on androgens is needed to clarify the strength of the androgen association, the differences in risk of hepatic tumors between the various androgen preparations, and the role of other risk factors known to contribute to liver neoplasms.

Despite these limitations, this review highlights several features of androgen therapy which are not generally well known. We identified a large number of androgen-treated patients without FA who developed liver tumors, supporting our first hypothesis. This group merits monitoring of their livers in a manner similar to that recommended for FA patients [1]. We found evidence in support of our second hypothesis, namely, that parenteral androgens may also be associated with an increased risk of liver tumors. This conclusion must be tempered by the fact that the patients in those reports may have had other, unidentified, risk factors, such as transfusions, hepatitis, or iron overload. In support of our third hypothesis that FA patients are more sensitive to androgens than non-FA patients, we found that FA patients developed their tumors at a younger age than either non-FA AA or non-AA patients. This is a consequence of the earlier age at which androgen treatment is initiated for AA in FA. Our fourth hypothesis was that the type of hepatic neoplasm is associated with the type of androgen. HCC were more frequent in patients who took oxymetholone or methyltestosterone than in those who took danazol. Because we do not know the size of the group receiving each type of androgen, this association requires further investigation. In addition, since there was an association between the choice of drug and the disorder for which it was used (for example, danazol was used only in non-AA patients), we cannot exclude confounding by indication. We are aware of a few unreported FA patients who are currently receiving danazol. It will be important to monitor those patients for liver tumors, as is done for patients on any form of anabolic androgenic steroids.

We recommend liver function tests at 2– to 3-month intervals and liver ultrasonography at least annually. Some of the tumors may regress if androgens are withdrawn, if bone marrow function permits, or a bone marrow transplant is performed [11,12,23,56]. In addition, patients who have completed any type of androgen therapy need to continue hepatic surveillance, since there is a risk of late development of liver tumors (up to 24 years) [81]. The non-FA patients in whom this occurred had no apparent alternative risk for liver tumors, although those with anemia might have had transfusions, iron overload, or viral exposures.

Despite the limitations inherent in a literature review, the cases of androgen-related hepatic neoplasms summarized here have permitted us to document that (a) patients with a broader spectrum of underlying disease than is usually considered are at risk of developing hepatic neoplasms and that (b) both HCC and adenomas may occur with any form of androgen, even those that are administered parenterally. Our summary raises the intriguing possibility that danazol may have a lower risk of HCC than other androgen preparations. More systematic and complete epidemiologic studies are required to precisely define the risks of androgen-related HCC and adenomas.

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